PATENT COOPERATION TREATY

DUE DATE

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/051431	30.03.2005	30.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/475, C12N15/12, A61K38/18, A61K31/7088, A61K31/713, A61P25/00, A61P37/00

Applicant
NsGene A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Authorized Officer

Madruga, J

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/051431

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 89-108 in respect of industrial applicability

because:

☒ the said international application, or the said claims Nos. 89-108 in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	77-88, 92-103, 105-107
	No:	Claims	1-76, 89-91, 104, 109-121
Inventive step (IS)	Yes:	Claims	77-88, 92-103, 105-107
	No:	Claims	1-76, 89-91, 104, 109-121
Industrial applicability (IA)	Yes:	Claims	1-88,109-121
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 89-108 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V. Reasoned statement with regard to novelty, inventive step or industrial applicability.

1. CITATIONS

1.1 Reference is made to the following documents:

D1: WO 01/39786 A (INNOGENETICS N.V; FRANSEN, LUCIA; DE BAETSELIER, PATRICK) 7 June 2001 (2001-06-07)

D2: WO 01/57190 A (HYSEQ, INC; TANG, Y., TOM; LIU, CHENGHUA; DRMANAC, RADOJE, T; ASUNDI,) 9 August 2001 (2001-08-09)

D3: WO 01/54474 A (HUMAN GENOME SCIENCES, INC; ROSEN, CRAIG, A; BARASH, STEVEN, C; RUBEN,) 2 August 2001 (2001-08-02)

D4: WO 01/83510 A (HUMAN GENOME SCIENCES, INC; KOMATSOULIS, GEORGE; RUBEN, STEVEN, M; ROS) 8 November 2001 (2001-11-08)

D5: NISHINO JINSUKE ET AL: "Meteorin: a secreted protein that regulates glial cell differentiation and promotes axonal extension" EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 23, no. 9, 5 May 2004 (2004-05-05), pages 1998-2008, XP002334608 ISSN: 0261-4189

D6: WO 2004/035732 A (FIVE PRIME THERAPEUTICS, INC; WILLIAMS, LEWIS, T; CHU, KETING; LEE, ER) 29 April 2004 (2004-04-29)

2. NOVELTY and INVENTIVE STEP (Art. 33(2) and (3) PCT)

2.1 D1 discloses human SMAF-2 (D1, figure 1) which has 100 % identity over 293 amino

acids (full length) with SEQ ID NO: 3 of the application. This document also discloses murine SMAF-2 (SEQ ID NO: 8) , which has 99.31 % identity to murine NsG33 of the present application in 288 amino acids overlap. D1 discloses nucleic acid molecules encoding for said polypeptides, vectors, host cells, antibodies, pharmaceutical compositions. Furthermore, D1 claims the use of SMAF-2 for the treatment of immunological disorders.

2.2 As can be seen from the above, document D1 discloses in combination all the features defined in independent claims **1, 22, 51, 56, 73, 74, 89, 108-110.** Hence the subject-matter of these claims is not new (Article 33(2) PCT).

2.3 D2 discloses a polypeptide (SEQ ID NO: 1401, pages 3665-3666) which has 100% identity over 293 amino acids with with SEQ ID NO: 3 of the application and a polypeptide (SEQ ID NO: 3369 page 314, GSP:AAM79723) with 98.44 % identity over 128 amino acids with SEQ ID NO: 3. D2 discloses medical uses of said polypeptide, including immune and nervous system disorders (pages 59-61).

2.4 D3 discloses a sequence, SEQ ID NO: 675 which has 98.61 % identity (98.61 % ungapped) over 216 amino acids (q:s=1-216:46-261) with SEQ ID No: 3 of the application. D3 discloses a polynucleotide, SEQ ID NO: 255, which has 97.19 % identity (97.98 % ungapped) over 748 nucleotides (q:s=13-760:36-778) with SEQ ID No: 2. D3 discloses medical uses of said polypeptide, including immune and nervous system disorders (paragraphs [0638-0655]).

2.5 D4 discloses SEQ ID NO: 93 and 94 (GENE NO: 21), which have 100 % identity over 103 amino acids (q:s=191-293:1-103) with SEQ ID No: 3 of the present application. SEQ ID NO: 31 of D4 has 100% identity over 421 nucleotides (q:s=688-1108:9-429) with SEQ ID NO: 2 of the application.

2.6 D2-D4 disclose all the features defined in independent claims **1, 22, 51, 56, 73, 74, 89, 108-110.** Hence the subject-matter of these claims is not new (Article 33(2) PCT).

2.7 Claims **2-21, 23-50, 52-55, 57-72, 75, 76, 90, 91, 104, and 111-121** do not contain any features which, in combination with the features of any claim to which they refer,

meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT) since they refer to embodiments which were disclosed in the prior art cited or represent obvious choices and alternatives for a skilled person in the technical field of the invention.

2.7.1 Concerning claims **113-121**, relating to fragments of the human, mouse and/or rat NsG33 polypeptide, comprising the carboxyl-terminal half, the amino-terminal half of NsG33 or missing the signal peptide, are not regarded as inventive since the human, murine and rat NsG33 polypeptides were known in the art (D1-D4) and said fragments do not have any special property or surprising effect which might render them inventive over the prior art. In addition, in view of the lack of any new functional and common structural features, there is no common concept linking each peptide fragment and, should the applicant pursue claims directed to such fragments, non-unity objections in the sense of Rule 13 PCT, might arise in the procedure.

2.8 Claims **77-88** and claims **92-103, 105-107** refer to specific uses of the polypeptide of the present invention or related reagents (polynucleotide, vector, host cells, biocompatible cell device or packaging cell line) for the manufacture of a medicament for the treatment of diseases or disorders associated with the nervous system. Although some of the above-mentioned prior art documents disclose general embodiments in the description concerning the use of polypeptides, including that of the present application, for diseases of the nervous system, it appears that said documents do not have sufficient disclosure of the specific use of the NsG33 peptide for treating diseases or disorders associated with the nervous system.

2.9 Thus, the combination of the features of claims **77-88, 92-103 and 105-107** does not appear to be known from, or rendered obvious by the available prior art.

3. INDUSTRIAL APPLICABILITY (Art. 33(2) and (3) PCT)

3.1 For the assessment of the present claims **89-108** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. Certain documents cited

4. Although D6 does not constitute prior art within the meaning of Rule 64.1(b), it appears to disclose all the features of claims 1-76,89-91,104,108-121. It might therefore be taken into consideration in the regional phase before the EPO. No check has been made as to wether the priority of this application has been validly claimed.

VIII Certain observations on the international application

5. SUFFICIENT DISCLOSURE (Art. 5 PCT)

5.1 The present application provides evidence that the secreted NsG33 polypeptide has an activity as a survival and growth factor for neurons. However, the applicant has not shown that the polypeptide of the invention has any real application in the treatment of a disease, disorder or damage of the nervous system. It appears that the skilled person would have an undue burden in determining, not only which of all the possible peptides claimed (e.g. in claim 1) is useful, but also would have an undue experimental burden to find out which of all the possible diseases named in the application (e.g. in claims 77-88 and 92-103). Thus, the subject-matter of claims 77-88 and 92-103 does not meet the requirements of Article 5 PCT because it lack sufficient disclosure.

6. CLARITY (Art. 6 PCT)

6.1 At present, there are too many independent claims and many claims which have

been drafted as separate independent claims, appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought or in respect of the terminology used for the features of that subject-matter. The present set of claims therefore lacks conciseness and as such does not meet the requirements of Article 6 PCT.